REMARKS

Amendments

Claims 12 and 13 have been cancelled, claims 1 and 11 have been amended, and claims 14 and 15 have been withdrawn. Upon entry of the amendment, claims 1-11 will be pending. Support for the added claims can be found in the specification, and in the claims as originally filed.

The specification has been amended to correct the priority date claim.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Rejections

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner argues that the term "SLC19A2" is indefinite.

As suggested by the Examiner, claim 1 has been amended to spell out solute carrier family 19 (thiamine transporter), member 2 in the first instance. Withdrawal is respectfully requested.

Claims 12 and 13 have been cancelled, without prejudice, rendering the rejections moot.

Rejections under 35 U.S.C. § 101/112, first paragraph

The Examiner has rejected claims 1-13 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility.

Applicant respectfully does not agree. Amended claim 1 is drawn to a transgenic mouse whose genome comprises a homozygous disruption in the endogenous solute carrier family 19 (thiamine transporter), member 2 (SLC19A2) gene, said mouse exhibiting, relative to a wild-type control mouse, a reproductive system abnormality. Claim 11 is similarly drawn to a mouse having a heterozygous disruption.

1. The Utility Requirement

Section 101 of the Patent Act of 1952, 35 U.S.C. § 101, provides that "whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," may obtain a patent on the invention or discovery.

According to the Federal Circuit:

> The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See Brenner v. Manson, 383 U.S. 519, 534, 16 L. Ed. 2d 69, 86 S. Ct. 1033 (1966); Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"); Fuller v. Berger, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

(*Juicy Whip v Orange Bang*, 185 F.3d 1364; 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999)(emphasis added)).

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.
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> . . .
>
> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)).

The standard for "credible" is defined as:

> . . . whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

(MPEP 2107.02, III(B)(emphasis added).

According to the Patent Office's own guidance to Examiners:

Langer and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. [citations omitted] . . . Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false.

Compliance with 35 U.S.C. 101 is a question of fact [citations omitted]. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. . . . To do this, Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art.

(MPEP 2107.02, III(A)(emphasis added).

Rejections under 35 U.S.C. 101 have been rarely sustained by federal courts. Generally speaking, in these rare cases, the 35 U.S.C. 101 rejection was sustained either because the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967). Special care therefore should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, of the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under 35 U.S.C. 101.

(MPEP 2107.02, III(B)(emphasis in original and added). The Guidelines additionally provide that:

There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather, the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed (citations omitted), and whether the asserted utility appears to contravene established scientific principles and beliefs. (citations omitted). Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." (citations omitted). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980)(reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court pointed out that a rigorous correlation is not necessary when the test is reasonably predictive of the response).

(MPEP 2107.02, VII)(emphasis added).

Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical

purpose. An assertion of utility is presumed to be true. The burden is on the Examiner to show that one of ordinary skill would find the asserted utility to be false. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, knockout mice have the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined.

According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
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> . . .
>
> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834)(emphasis added)(copy attached). Thus, the knockout mouse has been accepted by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible.

Knockout mice are so well accepted as tools for determining gene function that the director of the NIH Chemical Genomics Center of the National Human Genome Research Institute (among others, including Capecchi, Bradley, Joyner, Nagy and Skarnes) has proposed creating knockout mice for all mouse genes:

> Now that the human and mouse genome sequences are known, attention has turned to elucidating gene function and identifying gene products that might have therapeutic value. The laboratory mouse (Mus musculus) has had a prominent role in the study of human disease mechanisms throughout the rich, 100-year history of classical mouse genetics, exemplified by the lessons learned from naturally occurring mutants such as agouti, reeler and obese. The large-scale production and analysis of induced genetic mutations in worms, flies, zebrafish and mice have greatly accelerated the understanding of gene function in these organisms. Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.
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> . . .
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> A coordinated project to systematically knock out all mouse genes is likely to be of enormous benefit to the research community, given the demonstrated power of knockout mice to elucidate gene function, the frequency of unpredicted phenotypes in knockout mice, the potential economies of scale in an organized and carefully planned project, and the high cost and lack of availability of knockout mice being made in current efforts.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 921)(emphasis added)(copy attached).

More recently, the NIH announced it was accessing Deltagen's data derived from its analysis of the mice:

> "Our decision to procure these knockout mouse lines and data and make them available to the research community will yield tremendous benefits, both in the short and long terms," said NIH Director Elias A. Zerhouni, M.D. "This trans-NIH initiative will place important mouse models into the hands of researchers, speeding advances in the understanding of human disease and the development of new therapies. It also represents a significant step in the direction of launching an international project to systematically knock out all genes in the mouse."

> Since the early 1980s, when recombinant DNA technology was used to create the first such animals, knockout mice have proven to be one of the most powerful tools available to study the function of genes and to create mouse models of human disease. Researchers have produced knockout mice with characteristics similar to humans suffering from a wide range of disorders, including cancer, heart disease, neurological disorders and even obesity.

(See Researchers to Gain Wider Access to Knockout Mice Trans-NIH Effort Provides New Models for Understanding Human Disease; http://www.genome.gov/17015131) (copy attached).

Research tools such as knockout mice are clearly patentable, as noted by the Patent Office:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function), one that is clearly recognized by those skilled in the art.

For example, according to the Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)) (copy of relevant pages attached), one of the leading textbooks in the field of molecular biology:

> Extensive collaborative efforts are underway to generate comprehensive libraries of mutation in several model organisms including . . . the mouse. The ultimate goal in each case is to produce a collection of mutant strains in which every gene in the organism has either been systematically deleted, or altered such that it can be conditionally disrupted. Collections of this type will provide an invaluable tool for investigating gene function on a genomic scale.

(p. 543)(emphasis added).

According to Genes VII (Lewin, Oxford University Press (2000)) (copy of relevant pages attached), another well respected textbook in the field of genetics:

> The converse of the introduction of new genes is the ability to disrupt specific endogenous genes. Additional DNA can be introduced within a gene to prevent its

expression and to generate a null allele. Breeding from an animal with a null allele can generate a homozygous "knockout", which has no active copy of the gene. This is a powerful method to investigate directly the importance and function of the gene.

(p. 508)(emphasis added).

According to Joyner (Gene Targeting: *A Practical Approach*, Oxford University Press 2000) (copy of relevant pages attached),:

Gene targeting in ES cells offers a powerful approach to study gene function in a mammalian organism.

(preface)(emphasis added).

According to Matise et al. (*Production of Targeted Embryonic Stem Cell Clones* in Joyner, Gene Targeting: *A Practical Approach*, Oxford University Press 2000)(copy of relevant pages attached):

The discovery that cloned DNA introduced into tissue culture cells can undergo homologous recombination at specific chromosomal loci has revolutionized our ability to study gene function in cell culture and *in vivo*. . . . Thus, applying gene targeting technology to ES cells in culture affords researchers the opportunity to modify endogenous genes and study their function *in vivo*.

(p. 101)(emphasis added).

According to Crawley (What's Wrong With My Mouse *Behavioral Phenotyping of Transgenic and Knockout Mice*, Wiley-Liss 2000) (copy of relevant pages attached):

Targeted gene mutation in mice represents a new technology that is revolutionizing biomedical research.

Transgenic and knockout mutations provide an important means for understanding gene function, as well as for developing therapies for genetic diseases.

(p. 1, rear cover)(emphasis added).

2. Well-Established Utility

According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based

on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

Applicant submits that in light of arguments of record, a person of ordinary skill in the art would immediately appreciate why the invention is useful. Thus, it cannot be reasonably debated that a person of ordinary skill in the art would not immediately appreciate why the invention is useful: for determining gene function.

3. Substantial Utility

The Examiner argues that the asserted utilities are not substantial.

According to the MPEP:

A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. . . . the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

(A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved;

Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, e.g., Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

(MPEP § 2107.01 I)(emphasis added).

The MPEP additionally provides:

Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I).

A use is not substantial where further research is required to identify any use. This is not the case in the present application. Knockout mice have a well-known use in the study of gene function. In the present case, the instant invention does not require further research to establish a utility. Applicant has determined that SLC19A2 is associated with, for example, fertility. No further research is required to establish any use. Whether additional research is required to identify therapeutic agents targeting the SLC19A2 gene or to further characterize the function of the SLC19A2 gene is irrelevant to whether the claimed invention has satisfied the utility requirement (see, for example, *In re Brana*, "Usefulness in patent laws . . . necessarily includes the expectation of further research and development.")

Applicant submits that the specification teaches one how to use a mouse exhibiting reduced fertility. According to the specification (Example 4):

> As shown in Figure 5, when compared to age- and gender-matched wild-type control (+/+) male mice, as well as heterozygous mutant (+/-) male mice, homozygous mutant (-/-) male mice had decreased absolute combined testicular and epididymal organ weights.
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> As shown in Figure 6, when compared to age- and gender-matched wild-type control (+/+) male mice, as well as heterozygous mutant (+/-) male mice, homozygous mutant (-/-) male mice had decreased (organ to body weight ratio) combined testicular and epididymal organ weights, relative to body weight.
>
> These observations suggest a reproductive system abnormality, such as a genitourinary system abnormality like a testicular and/or epididymal abnormality.

The specification further provides (Example 5):

> When compared to age and gender-matched wild-type mice, homozygous mutant males exhibited a reproductive system abnormality, comprising testicular degeneration (comprising specifically degenerative changes of the seminiferous tubules of the testes), with corresponding marked hypospermatogenesis. There was an accompanying aspermia in the epididymides of these homozygous mutant males.

In addition to studying the role of the gene in fertility, the mice are useful for identifying agents capable of treating infertility. According to the specification:

> In one aspect of the present invention, a transgenic mouse having a disruption in the SLC19A2 gene exhibits a phenotype consistent with one or more symptoms of a disease associated with SLC19A2.
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> The present invention also provides methods of identifying agents capable of affecting a phenotype of a transgenic animal. For example, a putative agent is administered to the transgenic animal and a response of the transgenic animal to the putative agent is measured and compared to the response of a "normal" or wild-type mouse, or alternatively compared to a transgenic animal control (without agent

administration). The invention further provides agents identified according to such methods. The present invention also provides methods of identifying agents useful as therapeutic agents for treating conditions associated with a disruption or other mutation (including naturally occurring mutations) of the SLC19A2 gene.

One aspect of the present invention relates to a method of identifying a potential therapeutic agent for the treatment of a disease associated with the SLC19A2 gene, in which the method includes the steps of: administering the potential therapeutic agent to a transgenic mouse having a disruption in an SLC19A2 gene; and determining whether the potential therapeutic agent modulates the disease associated with the SLC19A2 gene, wherein the modulation of the disease identifies a potential therapeutic agent for the treatment of that disease.

A further aspect of the present invention provides a method of identifying a potential therapeutic agent for the treatment of a disease associated with the SLC19A2 gene, in which the method includes the steps of: contacting the potential therapeutic agent with SLC19A2 gene product; and determining whether the potential therapeutic agent modulates that product, wherein modulation of the gene product identifies a potential therapeutic agent for the treatment of the disease associated with the SLC19A2 gene.

The present invention further provides a method of identifying agents having an effect on SLC19A2 expression or function. The method includes administering an effective amount of the agent to a transgenic animal, preferably a mouse. The method includes measuring a response of the transgenic animal, for example, to the agent, and comparing the response of the transgenic animal to a control animal, which may be, for example, a wild-type animal or alternatively, a transgenic animal control. Compounds that may have an effect on SLC19A2 expression or function may also be screened against cells in cell-based assays, for example, to identify such compounds.

(page 4, lines 18 thru page 5, line 17). Transgenic mice of the present invention demonstrating the phenotype of reproductive abnormalities can be used, for example, to identify drugs capable of increasing fertility (an agonist) by comparing the effect of an agent on a wild-type control mouse with the transgenic mouse (i.e, as a negative control). If the compound causes a similar phenotype in a wild-type control mouse (i.e., in this case, increased fertility) but has no effect or reduced effect on the transgenic mouse, then the agent is selective for the SLC19A2 receptor.

Moreover, such knockout mice and methods of use are clearly patentable, as exemplified by U.S. Patent No. 6,444,873 (Edelman), which claims:

1. A transgenic mouse whose genome comprises a homozygous null mutation in the endogenous MSH5 gene, wherein said mouse exhibits abnormal development of the gonads.

2. An isolated cell, or a purified preparation of cells from a transgenic mouse whose genome comprises a homozygous null mutation in the endogenous MSH5 gene, wherein production of functional MSH5 is inhibited.

3. A method of evaluating a fertility treatment, comprising:
administering said treatment to a transgenic mouse whose genome comprises a null mutation in the endogenous MS5 gene, wherein said mouse exhibits abnormal development of the gonads and is infertile, and determining the effect of the treatment on fertility of said mouse, thereby evaluating said fertility treatment.

Applicant submits that, as demonstrated in the specification and published art, one of skill would know how to use the claimed invention to identify compounds capable of agonizing SLC19A2 activity which would be useful for the treatment of infertility.

In addition, the invention has a "real world use" as demonstrated by: (1) delivery of the claimed invention to at least one large pharmaceutical company (supporting affidavit or declaration available); and (2) commercial use of DeltaBase by three of the world's largest pharmaceutical companies, Merck, Pfizer and GlaxoSmithKline. DeltaBase incorporates the data set forth in the specification with regard to phenotypic analyses of the claimed mouse.

In *Raytheon*, the Federal Circuit held:

> A correct finding of infringement of otherwise valid claims mandates as a matter of law a finding of utility under § 101. *See e.g., E.I. du Pont de Nemours & Co. v. Berkley & Co., supra,* 620 F.2d at 1258-61, 205 USPQ at 8-11; *Tapco Products Co. v. Van Mark Products Corp.*, 446 F.2d 420, 428, 170 USPQ 550, 555-56 (6th Cir.), *cert. denied*, 404 U.S. 986, 92 S. Ct. 451, 30 L. Ed. 2d 370 (1971). The rule is not related, as Raytheon argues, to whether a defendant may simultaneously assert non-utility and non-infringement; a defendant may do so. The rule relates to the time of decision not to the time of trial, and is but a *common sense approach to the law*. ***If a party has made, sold, or used a properly claimed device, and has thus infringed, proof of that device's utility is thereby established***. *People rarely, if ever, appropriate useless inventions*.
>
> Proof of such utility is further supported when, as here, the inventions set forth in [the] claims . . . have on their merits been met with commercial success.

Raytheon Co. v. Roper Corp. 724 F. 2d at 959; see also, *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1327, 6 U.S.P.Q.2d 1065 (D. Del. 1987), *affirmed*, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1989)); *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)(a patent system must be related to the world of commerce rather than to the realm of philosophy). See also, *In re Fisher* 76 U.S.P.Q. 2d 1225 (Fed. Cir. 2005)(Fisher did not

present any evidence showing that agricultural companies have purchased or even expressed any interest in the claimed ESTs. And, it is entirely unclear from the record whether such business entities ever will.) Unlike *Fisher*, Applicant has submitted evidence that the claimed invention has been purchased and delivered to at least one large pharmaceutical company. Unlike *Fisher*, Appellant has presented evidence that the claimed knockout mouse has actually been used in the real world.

As held by the Federal Circuit, common sense dictates that "[i]f a party has made, sold, or used a properly claimed device, and has thus infringed, proof of that device's utility is thereby established. People rarely, if ever, appropriate useless inventions." *Raytheon Co. at* 959. As people rarely, if ever, appropriate useless inventions, large pharmaceutical companies, rarely if ever, purchase useless inventions.

Applicant respectfully submits that this evidence establishes the utility of the claimed invention.

4. Specific Utility

The Examiner states that the asserted uses are not specific.

According to the MPEP, "specific utility" means "specific" to the subject matter claimed as compared to a "general utility" that would be applicable to the broad class of the invention (MPEP 2107.01). Use of the SLC19A2 -/- and -/+ mice to study the function of the SLC19A2 gene and the association of the SLC19A2 gene with, for example, fertility, is specific to this mouse. Even if there were many other genes associated with these phenotypes, only the SLC19A2 knockout mouse (as opposed to all other knockout mice) would be used to study the specific role of this gene in fertility. The Examiner is respectfully requested to explain (1) how the asserted utility of determining the function of the SLC19A2 gene would be applicable to all other knockout mice; and (2) how the asserted use of studying the association of the SLC19A2 gene with infertility would be applicable to all other knockout mice. The Examiner is requested to explain how all other knockout mice would be used to study the function of the SLC19A2 gene.

5. In re Brana

Applicant submits that the legal principles as well as the facts of *Brana* are applicable to the present case. In *Brana*, the Board held that the applicant's specification failed to disclose a specific disease against which the claimed compounds were useful. The Federal Circuit reversed and held that the mouse tumor model represented a specific disease against which the compounds were effective. It is Applicant's position that a mouse demonstrating, for example, a reproductive abnormality, is sufficient to establish the animal's use as a model for studying and treating fertility disorders. As in *Brana*, confirmation of the phenotype in humans is unnecessary. In *Brana*, the PTO was aware of the asserted use against the mouse tumor lines but did not find the use specific – as in the present case:

> Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, see supra note 4, Paull grouped various benzo [de]isoquinoline-1,3-diones, which had previously been tested in vivo for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, 14 applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this particular type of cancer is much more specific than the vaguely intimated uses rejected by the courts in Kirk and Kawai. See, e.g., Cross v. Iizuka, 753 F.2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes -- sufficiently specific to satisfy the threshold requirement in Kirk and Kawai.)
>
> The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

(*Brana* at 1440). The court went on:

> The ultimate issue is whether the Board correctly applied the Section 112 Para.1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of Section 101, to the facts of this case. As we have explained, the issue breaks down into two subsidiary issues: (1) whether a person of ordinary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a

requirement that makes human testing a prerequisite to patentability under the circumstances of this case.

The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious decision.

The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.

If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

(*Brana* at 1443-44). The court's position is reflected in the MPEP: if an "assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility" (MPEP § 2107, II (A)(3); II (B)(1)).

6. Asserted Utility Supported by Those Skilled in the Art

Since the filing of Applicant's application, two separate parties have created mice having a disruption in the Slc19A2 gene.

Fleming *et al.* observed male -/- mice were infertile with reduced testes weight, suggesting "a previously unknown role for thiamin transport in spermatogenesis and male fertility." (*Mol.Gen.Metab.* 80 (2003) 234-241)(abstract).

Oishi *et al.* (Dev.Biol. 266 (2004) 299-309) similarly observed that male -/- mice were infertile and had reduced testes weight (p. 301). The data highlighted "an unexpected and critical role for thiamin transport and metabolism in spermatogenesis." (abstract).

Thus, those skilled in the art clearly understand how to make and use the claimed mouse.

7. Additional Examiner Arguments

The Examiner argues there is no correlation between the observed phenotypes and a disease or disorder (page 7).

Applicant submits that infertility is a specific disease or disorder. The knockout mice demonstrated reduced testes weight and aspermia compared with wild-type control mice. The phenotype was the result of the disruption. This is clearly supported by Fleming and Oishi. One skilled in the art would agree therefore that the Applicant has reasonably established that the SLC19A2 gene is associated with fertility.

The Examiner cites Olsen for the proposition that the phenotype of a knockout mouse could result from compensation by other proteins in the same pathway.

Applicant disagrees. First, whether the phenotype is a direct or indirect result of the disruption does not affect the utility of the mouse in determining the function of the gene, and is irrelevant to whether the claimed invention satisfies the utility requirement. The disruption ultimately results in the observed phenotype. The phenotypes of the claimed mice reveal that the SLC19A2 gene plays a role in fertility. The SLC19A2 KO mouse clearly is useful in elucidating the role SLC19A2 plays in these phenotypes. Applicant reminds the Examiner that Applicant is claiming a transgenic mouse, and not compounds or therapeutic methods related to the mouse or the targeted gene.

Further, Olsen's comments regarding compensation relate to the case when a knockout results in no apparent phenotype. Such is not the case here. Applicant has demonstrated that the disruption of the SLC19A2 gene results in a specific phenotype. Olsen does not provide any evidence or support for the position that the phenotype observed was a result of compensation by another protein in the same pathway, as suggested by the Examiner.

In fact, Olsen is supportive of Applicant's position that knockout mice are useful in determining the function of a target gene. Olsen describes knockout mice with null disruptions in several different subtypes of GABA receptors or related proteins. In each case, even with unexpected, lethal or a lack of phenotype, the mice revealed some role or function for the receptor subtype. Clearly, the knockout mice described were useful in determining the function of the GABA receptor.

In the conclusion, Olsen states "the use of mutant and knockout mice has aided understanding of the roles of GAD and GABAR in the intact mammalian organism, with much promise for additional information to come." (page 91). Even with respect to mice having

increased lethality, Olsen states: "[t]he γ2 and β3 subunit knockouts are associated with early postnatal lethality but have nonetheless provided considerable new information about their importance, including relevance to neurodevelopment, synaptogenesis, and possibly human disease. The β3 is a strong candidate for involvement in the epilepsy and other phenotypic attributes of Angelman syndrome, a human genetic disorder characterized by mental retardation, seizures, motor incoordination, and sleep disturbances. The γ2L knockout has allowed direct testing and negation of the selective subunit hypothesis for ethanol modulation of GABAR function. The δ subunit knockout appears to provide information about the function of GABAR in adult cerebellum, dentate gyrus of the hippocampal formation, and the thalamus. GAD_{65}, GABAR β3, and GABAR δ subunit knockouts all exhibit spontaneous seizures, but of different sorts, confirming suspicions that GABAR malfunction might produce epilepsy by more than one mechanism and providing excellent animal models for investigation of the cause of the seizure phenotype." (page 91-92).

Olsen goes on to say: "[i]n summary, transgenic and knockout mice have demonstrated that GABA plays a major role in brain development, control of palate formation, and epileptogenesis via multiple mechanisms." (page 92). It is untenable to cite Olsen as standing for the proposition that knockout mice do not have a well-accepted use in determining gene function.

Applicant notes that the Examiner has provided no evidence of the existence of such compensatory processes with respect to the SLC19A2 mutation claimed and therefore the Examiner has failed to show that it is more likely than not that person skilled in the art would not consider credible any specific and substantial utility asserted by Applicant. See MPEP §2107.II(C)(2). Assuming, *arguendo*, that such compensatory processes do indeed occur, Crawley (1996) Trends Neurosci. 19:181-182 notes that "[f]rom the point of view of developmental biology, the compensatory process is a fascinating study unto itself. In cases where the knockout mice appear to be phenotypically normal, we have the opportunity to learn a great deal about genetic redundancy and alternative biochemical pathway." Thus, even if such compensatory processes do indeed result from the null mutation - which is pure speculation at this point - then this establishes an additional utility for the claimed mice, namely the study of those compensatory processes.

The Examiner argues that background and the "hitchhiker" alleles can have an effect on the resulting phenotype, citing Mogil, Leonard and Sigmund.

The Examiner's position is based on conjecture as there is no evidence that the claimed invention is affected by a hitchhiker allele. Moreover, the Examiner cannot presume a general proposition based on a rare phenomenon. According to Wolfer *et al.*,: "..the possibility exists that an apparent effect of a null mutation could be due to a flanking 129 gene. Generally, the problem is disregarded because it imposes control strategies deemed costly, and because the statistically expected number of confounding flanking genes is relatively low" (emphasis added) (2002, *TRENDS in Neuroscience*, 25:336-340; page 336)(copy attached). Thus, hitchhiker alleles are a rare phenomenon. A "rare phenomenon" does not show that it is more likely than not that person skilled in the art would not consider credible any specific and substantial utility asserted by Applicant. See MPEP §2107.II(C)(2).

Applicant submits that one skilled in the art would accept that the phenotypes are due to the disruption in the targeted gene. This is supported by the fact that (1) after each conducted extensive due diligence, Merck, Pfizer and GlaxoSmithKline subscribed to DeltaBase; (2) the claimed invention has been provided to at least one large pharmaceutical company; and (3) the NIH has elected to obtain access to Deltagen's data and mice within DeltaBase, with regard to which the NIH has publicly stated:

> "The process used by NIH to select the mouse lines involved a rigorous scientific review process that evaluated information on the knocked out gene, the reliability of the method used to produce the knockout, and whether the mouse line possesses a "reporter" gene, which enables researchers to analyze the pattern of the knockout gene's expression in various mouse tissues."

(See Researchers to Gain Wider Access to Knockout Mice Trans-NIH Effort Provides New Models for Understanding Human Disease; http://www.genome.gov/17015131) (copy attached).

Applicant respectfully submits that in light of the overwhelming evidence, it is unreasonable to argue that (1) the invention lacks utility; and (2) that one skilled in the art would not know how to use the claimed knockout mouse.

8. Summary

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the transgenic mice are useful for studying SLC19A2 gene function with respect to the cited phenotypes, expression analysis and are therefore useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly made a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant to be specific and substantial. (*In re Brana*; MPEP § 2107).

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-13 are rejected because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility for the reasons set forth in the utility rejection. Applicants respectfully traverse the rejection. For the reasons set forth above, the claimed invention satisfies the utility requirement. Therefore, one skilled in the art would know how to use the invention.

Claims 12 and 13 have been rejected as allegedly failing to comply with the enablement requirement.

The claims have been canceled, rendering the rejection moot.

Claims 11-13 have been rejected as encompassing chimeric mice.

The claims have been amended to reflect a genomic disruption.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 12 and 13 have been rejected as allegedly failing to comply with the written description requirement.

The claims have been canceled, rendering the rejection moot.

In view of the above amendments and remarks, Applicant respectfully requests reconsideration and a Notice of Allowance. If the Examiner believes a telephone conference

would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. **502775**.

Respectfully submitted,

6-7-06
Date

JER

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